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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY	DOCKETING
097425,633	10/22/99	CHIEF	M	FORM

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EXAMINER

ART UNIT

PAPER NUMBER

08/16/01

DATE MAILED:

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

**Advisory Action**

Application No.

09/425,633

Applicant(s)

CHEE ET AL.

Examiner

BJ Forman

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 August 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation of Advisory Action.

3. ☒ Applicant's reply has overcome the following rejection(s): 35 U.S.C. 112, second paragraph.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: \_\_\_\_\_.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 17-41.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☐ Other:

**Continuation of Advisory Action****Response to Arguments**

Applicant argues that Nikiforov et al. does not teach microspheres on the surface of a substrate, Walt et al. does not explicitly teach methods for genotyping and neither reference teaches or suggests combining their teachings and therefore the examiner has failed to set forth a prima facie case of obviousness. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Nikiforov et al. teach a method comprising: providing a hybridization complex comprising a target sequence, a first oligonucleotide and a second oligonucleotide, adding a composition comprising a polymerase, a ligase and NTP mixture to allow the incorporation of the NTP to detect and identify the nucleotide at a detection position wherein the first oligonucleotide is attached to a microsphere (Columns 6-7 and Column 11, lines 6-8) wherein the method comprises a plurality of detection probes (Example 1, Column 16, line 55-Column 17, line 1) and wherein the label comprises a functional group for addition of a fluorophore (Column 13, lines 41-50). While Nikiforov et al. do not teach the microsphere is on a surface of a substrate, and they do not teach each NTP comprises a unique fluorophore, Walt et al. teach the similar method wherein the microsphere is on a surface and each detection comprises a unique fluorophore (Column 4, lines 1-14) and they teach a motivation to modify the microsphere-attached oligonucleotide of Nikiforov et al. i.e. because the microspheres are arrayed on the surface of the support, the signal generation is "extremely uniform" allowing automatic analysis within seconds using commercially

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available software (Column 4, lines 20-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the microsphere-attached oligonucleotides of Nikiforov et al. by arraying the microspheres on the surface of a substrate as taught by Walt et al. for the benefits of economy and uniform signal detection as taught by Walt et al. (Column 4, lines 20-27).

Applicant argues that the teaching of Lyamichev et al. operates to change to principle of operation of Nikiforov et al. and therefore the teachings of the references are insufficient to render the claims obvious. This argument is not found persuasive because the principle operation of Nikiforov et al. is the detection of a nucleotide at a specific site (Column 6, lines 40-44) and functions by providing hybridization complex comprising a target sequence, a first oligonucleotide and a second oligonucleotide, adding a composition comprising a polymerase, a ligase and NTP, wherein the first oligonucleotide is attached to a microsphere (Columns 6-7 and Column 11, lines 6-8). Lyamichev et al. teach a similar method having the principle operation of detecting a nucleotide at a specific site wherein the hybridization complex is contacted with a cleavage enzyme which enhances specificity of detection and allows single-base discrimination of multiple sites from a single sample (page 295, left column, second full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the ligase mediated site-specific detection of Nikiforov et al. with the cleavage-mediated detection taught by Lyamichev et al. for the benefit taught by the latter i.e. enhanced specificity of detection and single-base discrimination of multiple site (page 295, left column, second full paragraph). Therefore, applying the cleavage enzyme mediated detection of Lyamichev et al. would enhance, not change the principle of operation of Nikiforov et al.


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**Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

  
BJ Forman, Ph.D.  
August 28, 2001

  
S. Forman  
Stephanie E. Forman  
Principal Examiner